Application No.: 10/618,573

I hereby certify that this correspondence is being deposited with the U.S. Postal Service with sufficient postage as First Class Mail, in an envelope addressed to: MS Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date shown below.

Dated: _____ Signature: _____ (Judy Calem)

Docket No.: 219002030100

Docket No.: 219002030100
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Babu J. MAVUNKEL et al.

Application No.: 10/618,573 Confirmation No.: 3779

Filed: July 11, 2003 Art Unit: 1625

For: IMPROVED REAGENTS FOR N-AMINATION Examiner: S. Perlinger

DECLARATION OF CHEMIST / INVENTOR UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Richland Tester, declare as follows:

1. I am one of the chemists listed as an inventor on U.S. patent application No. 10/618,573. I have a Ph.D. degree in chemistry, and have worked in the field of organic chemistry for __ years. A copy of my *curriculum vitae* is attached as **Exhibit B**.

2. I have reviewed the specification and the claims currently pending in the above-referenced case. I understand that the Patent Examiner rejected the pending claims because the claim term "recipient compound", as used in claims 8 and 10, was not considered clear.

3. I understand that the standard to be applied in assessing the clarity of claim language asks whether the term would have been understood by one of ordinary skill in view of the entire patent application.

4. From my experience as a practicing organic chemist, I state that in the context of this application, the term "recipient compounds" would have been understood by one of ordinary skill to refer to compounds that could be N-aminated by the aminating agents described in the application, like the indole that is aminated in the examples.

5. I also state that, based on reading the application, one of ordinary skill would expect the aminating agents described in the application to be capable of aminating the same types of compounds that were known to be aminated by analogous aminating agents known in the art, which are those aminating agents that operate by transferring $-NH_2$ from $-O-NH_2$ in the aminating agent to N in a compound to be aminated. I believe that such a compound to be aminated could accurately be described as a 'recipient compound.'

6. I also am aware that analogous aminating agents and their amination reactions were known in the art at the time the application was filed, some of which are mentioned in the application. Based on that information and knowledge, the term 'recipient compound' would have been understood to refer to the types of compounds that were then known to be aminated by analogous aminating agents that transfer $-NH_2$ from $-O-NH_2$ in the aminating agent to N in a recipient compound, like the aminating reagent described in the application does.

7. I also understand that the Patent Examiner rejected the claims because certain conditions such as the reaction temperature were not specified.

8. From my experience, I state that a chemist reading a description of a reaction where no temperature was specified would understand that the reaction was performed at ambient temperature, and would also understand that the precise temperature was not critical.

9. I further state that where a particular chemical transformation such as N-amination is well known, and an improved agent is introduced for performing that transformation, one of ordinary skill would know to use conditions that worked for such known transformations as guidance when selecting conditions for using the improved agent. Using such guidance, selection of suitable reaction conditions for using the improved agent would be a routine matter unless, the improved agent appeared to operate by a different chemical mechanism. In this case, analogous aminating agents that operate by transferring $-NH_2$ from $-O-NH_2$ in the aminating agent to N in a recipient compound were known in the art; thus the generally available knowledge about N-amination reactions would enable the ordinary chemist to use the improved aminating agents in the application to aminate compounds that were known to be aminated by analogous aminating agents.

I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Executed at Fremont (city), CA (state), on 5 (day) May (month) 2006.

Richland W. Tester

sd-314501

CURRICULUM VITAE

Richland Tester
2020 Pacific Ave.
Alameda, CA 94501

EDUCATION

School	Date	Major/Minor Courses	Degree
University of California NIH Post-Doc with Prof. Neal Schore	2/95– 1/97	Natural Product synthesis	Post-Doc
University of Utah	6/89 – 1/95	Synthetic Organic Chemistry	PhD
Texas Lutheran College	1/85-5/89	Chemistry	BS/BA

EMPLOYMENT HISTORY (most recent first)

Scios, Inc. 3/2000-present

- Manage chemistry outsourcing for medicinal chemistry group
  - Oversee the work of 19 chemist
  - Manage resources at 4 compnies in Europe and India
- P38 chemistry team lead
  - Interact with various groups in the biological sciences
  - Stragtegic oversight of the chemistry efforts on the p38 program at Scios
- Synthesis of targeted at inhibition of p38 MAP kinase

Ribogene, Inc 2/1999 – 2/2000

- Antibacterials
  - Synthesis of compounds with antibacterial properties

Chiron, Inc. 2/1997 - 2/1999

- Hepititis C antivirals
  - Synthesize inhibitors of HepC protease
  - Synthesize inhibitors of HepC helicase

Abstracts of N-Amination Reactions

Comparison of Electrophilic Amination Reagents for N-Amination of 2-Oxazolidinones and Application to Synthesis of Chiral Hydrazones. Shen, Yuehai; Friestad, Gregory K. Department of Chemistry Cook Physical Science Building, University of Vermont, Burlington, VT, USA. Journal of Organic Chemistry (2002), 67(17), 6236-6239. Publisher: American Chemical Society, CODEN: JOCEAH ISSN: 0022-3263. Journal written in English. CAN 137:232577 AN 2002:539087 CAPLUS (Copyright (C) 2006 ACS on SciFinder (R))

Abstract

Comparison of several hydroxylamine-based electrophilic ammonia equiv. in the N-amination of 2-oxazolidinones revealed that O-(p-nitrobenzoyl)hydroxylamine (NbzONH2) and sodium hydride in dioxane is a superior reagent combination for this purpose. Practical prepns. of a variety of chiral N-acylhydrazones by this method gave yields ranging from 45 to 95%. Methods for exchange or removal of the aldehyde component have been developed, making this a general route to chiral N-acylhydrazones of interest for asym. synthesis applications.

Electrophilic N-Amination of Two Quinazoline-2,4-diones Using Substituted (Nitrophenyl)hydroxylamines. Boyles, David C.; Curran, Timothy T.; Parlett, Roger V., IV; Davis, Mark; Mauro, Frank. Chemical Research and Development, Pfizer Global Research and Development, Ann Arbor, MI, USA. Organic Process Research & Development (2002), 6(3), 230-233. Publisher: American Chemical Society, CODEN: OPRDFK ISSN: 1083-6160. Journal written in English. CAN 136:386091 AN 2002:227358 CAPLUS (Copyright (C) 2006 ACS on SciFinder (R))

Abstract

The prepn. of a few (nitrophenyl)hydroxylamines and reaction with two quinazoline-2,4-diones is described. The electrophilic aminating agents were assessed in terms of yield for the N-amination of two quinazoline-2,4-diones and safety considerations for rapid scale-up. For the amination of the described system, the best yield and the highest onset temp. were found in the same aminating agent, specifically, (4-nitrophenyl)hydroxylamine.

Preparation of (aminoureido)crotonamides as intermediates for aminouracils. Shimoharada, Hiroshi; Kishiro, Nobuko. (Ishihara Sangyo Kaisha, Ltd., Japan). Jpn. Kokai Tokkyo Koho (2002), 6 pp. CODEN: JKXXAF JP 2002167374 A2 20020611 Patent written in Japanese. Application: JP 2000-365424 20001130. Priority: . CAN 137:20229 AN 2002:436701 CAPLUS (Copyright (C) 2006 ACS on SciFinder (R))

Patent Family Information

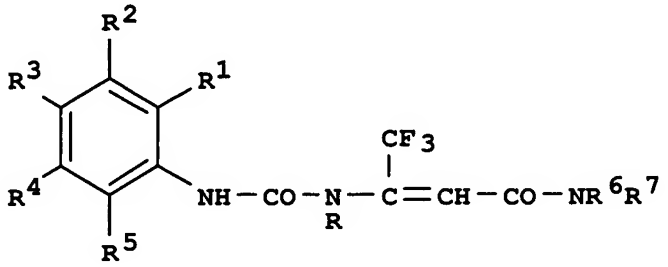
Patent No.	Kind	Date	Application No.	Date
JP 2002167374	A2	20020611	JP 2000-365424	20001130

Priority Application	
JP 2000-365424	20001130

Abstract

(aminoureido)crotonamides I [R = NH2; R1-R5 = H, halo, cyano, (un)substituted alkyl, (un)substituted alkoxy, (un)substituted aryloxy, etc.; R6, R7 = alkyl; R6R7 may be alkylene], useful as intermediates for

pesticides or drugs, are prepd. by amination of ureidocrotonamides I (R = H; R1-R7 = same as above). Thus, 3.54 g 3-[4-chloro-2-fluoro-5-(4-nitrophenoxy)phenylcarbamoylamino]-4,4,4-trifluoro-N,N-dimethylcrotonamide was aminated by O-(2,4-dinitrophenyl)hydroxyamine in DMF in the presence of K2CO3 to give 2.45 g of the corresponding aminoureide deriv.



I

Preparation of 1-amino-3-phenyluracils by amination with O-mesitylenesulfonylhydroxylamine. Andree, Roland; Hoischen, Dorothee; Hupperts, Achim; Linker, Karl-heinz; Weintritt, Holger; Wroblowsky, Heinz-juergen. (Bayer A.-G., Germany). Ger. Offen. (2001), 12 pp. CODEN: GWXXBX DE 10005284 A1 20010809 Patent written in German. Application: DE 2000-10005284 20000207. Priority: . CAN 135:152819 AN 2001:579186 CAPLUS (Copyright (C) 2006 ACS on SciFinder (R))

Patent Family Information

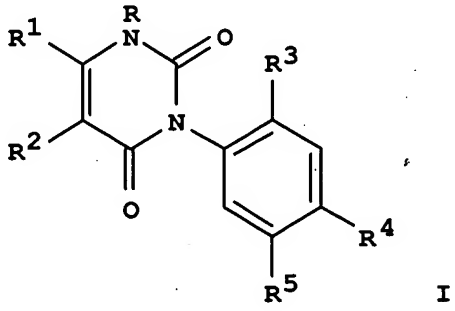
Patent No.	Kind	Date	Application No.	Date
DE 10005284	A1	20010809	DE 2000-10005284	20000207
WO 2001058883	A1	20010816	WO 2001-EP795	20010125
		W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM		
		RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG		
EP 1257540	A1	20021120	EP 2001-902351	20010125
		R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR		
JP 2003522762	T2	20030729	JP 2001-558434	20010125
US 2003032807	A1	20030213	US 2002-182966	20020802

Priority Application		
DE 2000-10005284	A	20000207
WO 2001-EP795	W	20010125

Abstract

Title compds. [I; R = NH2; R1 = (substituted) alkyl; R2 = H, NO2, cyano, halo, (substituted) alkyl; R3 = H, NO2, cyano, halo; R4 = H, NO2, cyano, carbamoyl, thiocarbamoyl, OH, halo, (substituted) alkyl, alkoxy, benzoyloxy; R5 = H, OH, SH, amino, hydroxyamino, NO2, cyano, CO2H, carbamoyl, thiocarbamoyl, halo, R6, QR6, NHR6, NHOR6, NHSO2R6, N(SO2R6)2, etc.; Q = O, S, SO, SO2; R6 = (substituted) alkyl,

alkenyl, alkynyl, cycloalkyl, etc.], were prepd. by treatment of I (R = H) with O-mesitylenesulfonylhydroxylamine (II) optionally in the presence of auxiliary agents and solvents at -50° to 80°. Thus, I [R = H; R1 = CF3; R2 = H; R3 = F; R4 = Br; R5 = NO2] in AcOEt was stirred with NaHCO3, Na2SO4, and II at room temp. to give 77.5% I [R = NH2, R1 = CF3; R2 = H; R3 = F; R4 = Br; R5 = NO2].

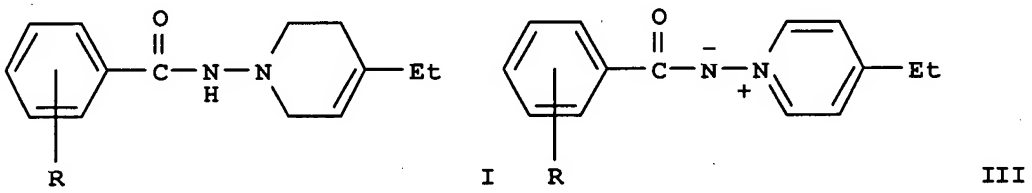


I

Synthesis of N-(substituted phenylcarbonylamino)-4-ethyl-1,2,3,6-tetrahydropyridines as potential nonsteroidal anti-inflammatory agents. Yoon, Kyoung Jin P.; Kode, Bala; Bowen, Lynneice; Redda, Kinfe K. College of Pharmacy and Pharmaceutical Sciences, Florida A and M University, Tallahassee, FL, USA. Journal of Heterocyclic Chemistry (2001), 38(1), 69-76. Publisher: HeteroCorporation, CODEN: JHTCAD ISSN: 0022-152X. Journal written in English. CAN 135:76754 AN 2001:223203 CAPLUS (Copyright (C) 2006 ACS on SciFinder (R))

Abstract

Fourteen (phenylcarbonylamino)ethyltetrahydropyridines I (R = MeO, Me, Cl2, F3C, Et, Bu, Me3C, F, Br) were prepd. in fair to good yields. Thus, 4-Ethylpyridine reacted with O-mesitylenesulfonylhydroxylamine to furnish N-amino-4-ethylpyridinium mesitylenesulfonate (II). Reaction of II with benzoic acid chlorides RC6H4COCl gave the stable cryst. pyridinium ylides III. NaBH4 redn. of III in EtOH gave I in 26-83% yields.



I III

A convenient procedure for N-amination of 4-oxo-1,4-dihydroquinolines. Edmont, Dolores; Buisson, Yvon; Treillard, Philippe; Plisson, Christophe; Chenault, Jacques. Institut de Chimie Organique et Analytique, Universite d'Orleans, Orleans, Fr. Synthetic Communications (2000), 30(2), 217-225. Publisher: Marcel Dekker, Inc., CODEN: SYNCAV ISSN: 0039-7911. Journal written in English. CAN 132:251060 AN 2000:116199 CAPLUS (Copyright (C) 2006 ACS on SciFinder (R))

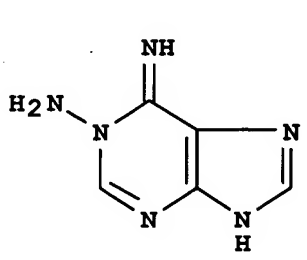
Abstract

A high-yielding N-amination of quinolones at low temp. via the use of O-mesitylenesulfonylhydroxylamine is reported.

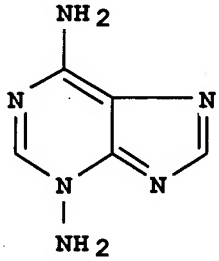
Electrophilic amination of adenines. Formation and characteristics of N-aminoadenines. Saga, Tetsuya; Kaiya, Toyo; Asano, Shoji; Kohda, Kohfuku. Faculty of Pharmaceutical Sciences, Nagoya City University, Nagoya, Japan. Nucleosides & Nucleotides (1996), 15(1-3), 219-33. Publisher: Dekker, CODEN: NUNUD5 ISSN: 0732-8311. Journal written in English. CAN 124:289077 AN 1996:109069 CAPLUS (Copyright (C) 2006 ACS on SciFinder (R))

Abstract

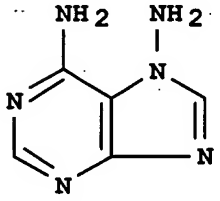
Amination of adenine with H2N-O-SO3H in alk. media afforded 1- (I), 3- (II), 7- (III) and 9-aminoadenine (IV) isomers at a ratio of about 1:1:3:1. In neutral media, the product ratio of the isomers changed to about 3:1:1:0. These results were different from the regioselectivity obtained by methylation of adenine with di-Me sulfate under similar conditions. Amination of adenine with dinitrophenoxyamine in DMF gave 1-aminoadenine as the main product and this regioselectivity was also different from that of methylation with CH3I. Chem. characteristics of these N-amino adenines are described.



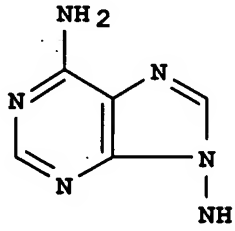
I



II



III



IV

Preparation of N-alkyl-N-pyridinyl-1H-indol-1-amines via arylation of 1-amino-3-haloindoles with halopyridines followed by alkylation and dehalogenation. Lee, Thomas B.; Goehring, Keith E. (Hoechst-Roussel Pharmaceuticals Inc., USA). U.S. (1995), 7 pp. CODEN: USXXAM US 5459274 A 19951017 Patent written in English. Application: US 94-242395 19940513. Priority: . CAN 124:145914 AN 1995:951498 CAPLUS (Copyright (C) 2006 ACS on SciFinder (R))

Patent Family Information

Patent No.	Kind	Date	Application No.	Date
US 5459274	A	19951017	US 1994-242395	19940513
EP 683165	A2	19951122	EP 1995-106921	19950508
EP 683165	A3	19970115		
EP 683165	B1	20000802		
		R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE		
AT 195120	E	20000815	AT 1995-106921	19950508

PT 683165	T	20001229	PT 1995-106921	19950508
ES 2152342	T3	20010201	ES 1995-106921	19950508
AU 9517997	A1	19951123	AU 1995-17997	19950511
AU 697090	B2	19980924		
CA 2149286	AA	19951114	CA 1995-2149286	19950512
JP 07304768	A2	19951121	JP 1995-114468	19950512
US 5644062	A	19970701	US 1995-455468	19950531
US 6512125	B1	20030128	US 1995-455469	19950531
GR 3034751	T3	20010228	GR 2000-402441	20001102

Priority Application

US 1994-242395	A	19940513

Abstract

A process is claimed for the prepn. of memory enhancing, analgetic, and antidepressant N-alkyl-N-pyridinyl-1H-indol-1-amines I wherein R is hydrogen, loweralkyl, loweralkoxy or trifluoromethyl; R1 is hydrogen or loweralkyl; R2 is loweralkyl; R3 is hydrogen, loweralkyl, loweralkoxy or trifluoromethyl; and m is 1 or 2, which comprises the steps of: (a) reacting a compd. of the formula II wherein R, R1 and m are as above with an N-X-succinimide wherein X is bromo, chloro or iodo to provide a compd. of the formula III wherein R, R1, X and m are as above; (b) reacting the compd. obtained in step (a) with a compd. of the formula H2NOSO3H to provide a compd. of the formula IV wherein R, R1, X and m are as above; (c) reacting a compd. obtained in step (b) with a compd. of the formula V wherein R3 is as above and Y is chloro, bromo or iodo to provide a compd. of the formula VI wherein R, R1, R3, X and m are as above; (d) reacting a compd. obtained in step (c) with a compd. of the formula R2Z wherein R2 is as above and Z is bromo or chloro to provide a compd. of the formula VII wherein R, R1, R2, R3, X and m are as above; (e) reacting a compd. obtained in step (d) with formic acid in the presence of a metal catalyst; and (f) isolating the product. The following reaction sequence was provided: (a) indole + N-chlorosuccinimide → 3-chloroindole (92.9%); (b) 3-chloroindole + hydroxylamine-O-sulfonic acid → 3-chloro-1H-indol-1-amine (86%); (c) 3-chloro-1H-indol-1-amine + 4-chloropyridine.HCl → 3-chloro-N-4-pyridinyl-1H-indol-1-amine salicylate (48.4%); (d) 3-chloro-N-4-pyridinyl-1H-indol-1-amine salicylate + 1-bromopropane → 3-chloro-N-propyl-N-4-pyridinyl-1H-indol-1-amine hydrochloride (87.6%); (e) dehalogenation of 3-chloro-N-propyl-N-4-pyridinyl-1H-indol-1-amine hydrochloride with NEt3, 5% Pd/C, and formic acid to afford N-propyl-N-4-pyridinyl-1H-indol-1-amine (79.5%); (f) conversion to the HCl salt (88.6%).

Synthesis of pyrrolo[2,1-f][1,2,4]triazine congeners of nucleic acid purines via the N-amination of 2-substituted pyrroles. Patil, Shirish A.; Otter, Brian A.; Klein, Robert S. Albert Einstein Coll., Medicine Cancer Cent., Bronx, NY, USA. Journal of Heterocyclic Chemistry (1994), 31(4), 781-6. CODEN: JHTCAD ISSN: 0022-152X. Journal written in English. CAN 122:9999 AN 1995:51452 CAPLUS

Abstract

The synthesis of several new 4-mono- and 2,4-disubstituted pyrrolo[2,1-f][1,2,4]triazines is described. Key intermediates 1-aminopyrrole-2-carbonitrile (3) and 1-amino-5-ethylpyrrole-2-carbonitrile (15) were obtained by N-amination of the corresponding pyrrole-2-carboxaldehyde followed by CHO → CN conversion with either hydroxylamine-O-sulfonic acid for 3 or O-mesitylenesulfonylhydroxylamine for 15. Cyclization of 3 or 15 with a variety of amidine reagents or, after conversion of 3 to its corresponding amide, base-catalyzed annulation completed the synthesis of the title products.

Synthesis and properties of N-aminoguanines. Kohda, Kohfuku; Yasuda, Moriyoshi; Ukai, Hiroshi; Baba, Kunihisa; Yamagata, Yuriko; Kawazoe, Yutaka. Fac. Pharm. Sci., Nagoya City Univ., Nagoya, Japan. Tetrahedron (1989), 45(20), 6367-74. CODEN: TETRAB ISSN: 0040-4020. Journal written in English. CAN 113:23492 AN 1990:423492 CAPLUS (Copyright (C) 2006 ACS on SciFinder (R))

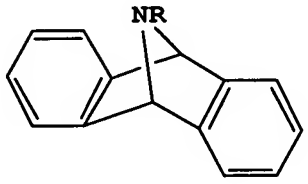
Abstract

1-, 3-, 7-, And 9-aminoguanines, and 1,7-, and 3,7-diaminoguanines, were prepd. starting with deoxyguanosine or O6-methylguanine and with H2NOSO3H or 2,4-(O2N)2C6H3ONH2. Physicochem. characteristics of these N-aminoguanines are described.

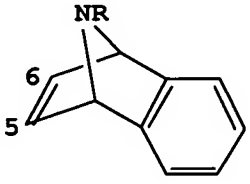
Synthesis, characterization, and thermolysis of 7-amino-7-azabenzonorbornadienes. Carpino, Louis A.; Padykula, Robert E.; Barr, Donald E.; Hall, Frances H.; Krause, Josef G.; Dufresne, Richard F.; Thoman, Charles J. Dep. Chem., Univ. Massachusetts, Amherst, MA, USA. Journal of Organic Chemistry (1988), 53(11), 2565-72. CODEN: JOCEAH ISSN: 0022-3263. Journal written in English. CAN 108:221540 AN 1988:221540 CAPLUS (Copyright (C) 2006 ACS on SciFinder (R))

Abstract

Treatment of N-benzylisoindole with benzyne, generated from o-BrC6H4F with Mg in THF, gave dibenzoazanorbornadiene I (R = CH2Ph). NBS-mediated debenzylation-bromination followed by reaction with N2H4 gave I (R = H), which was aminated with H2NO3SC6H2Me3-2,4,6 to give I (R = NH2) (II). Similar amination of benzoazanorbornadiene III (R = H) gave III (R = NH2) (IV), which was unstable, and was isolated as III [R = (9-fluorenylmethoxy)carbonyl]. IV underwent self-redn. to its 5,6-dihydro deriv. upon standing overnight in Et2O. IV reacted with PhC.tplbond.CCO2Et in Et2O to give PhCH2CH2CO2Et and both (Z)- and (E)-PhCH:CHCO2Et. Thermolysis of both II and IV in the presence of PhC.tplbond.CCO2Et in Et2O contg. AcOH gave only (Z)-PhCH:CHCO2Et. These results suggest that under acidic conditions both II and IV decomp. to HN:NH2+, while under neutral conditions IV gives H2N+:N- alone or as a mixt. with HN:NH. Thermolysis of II in HCONMe2 gives 87% 9,10-dihydroanthracene; in C6H6, CHCl3, or THF, II gives complex mixts.



I



III